EXHIBIT IV

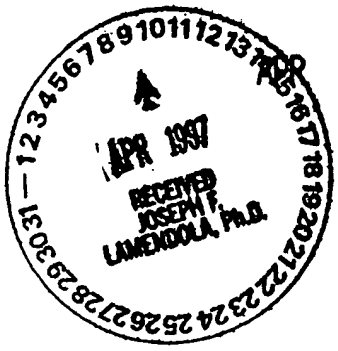
FDA LETTER PLACING IND # 52,791 ON CLINICAL HOLD AND SCHERING RESPONSE TO IND HOLD

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 52,791



4 1997

Schering Corporation
Attention: Joseph F. Lamendola, Ph.D.
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola:

Please refer to your Investigational New Drug Application (IND) submitted February 28, 1997, pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for SCH 58235 capsules.

We also refer to the March 31, 1997, telephone conversation in which you were notified that the study you propose under your IND may not be initiated because of deficiencies under 21 CFR 312.42(b)(iv). The information provided is insufficient, under 21 CFR 312.23, to allow us to assess the risk to subjects of the proposed studies. Summarized below are the specific deficiencies and the information needed to resolve these deficiencies.

Clinical Hold deficiencies

The results from both clinical studies with SCH 58235 are preliminary and incomplete. This is of particular concern for this product because:

1. It appears that the product has a long half-life (≥ 24 hours) based on single dose pharmacokinetics (multidose PK data were not provided). The half-life could not be calculated by conventional methods due to prolonged absorption and significant enterohepatic recycling.

2. Drug (both unchanged and total) was still detectable in the plasma 72 hours after a single 50 mg dose.

3. Preliminary safety data indicate that the drug is hepatotoxic and the data submitted indicate that liver transaminase returns to baseline only after 10 days to 3 weeks after the drug (administered as either a single dose or up to only 14 days) is discontinued. The hepatotoxicity does not appear to be dose-related and the degree of SGPT elevation is clinically significant (up to 4 times ULN). Of particular note, it took 3 weeks for liver function tests to return to normal in one patient who received a single 5 mg dose of the drug.

Also, treament was discontinued in another subject after only 10 days of SCH 58235 50 mg, due to a 4-fold rise in SGPT from baseline, with the level 4 times ULN on the drug.

Information needed to resolve clinical hold deficiencies

1. Final and complete safety and pharmacokinetic data must be submitted. The efficacy data would also be of interest.

2. Please submit the safety guidelines for study drug discontinuation, the results of your interim analysis, and a curriculum vitae for each of the investigators.

In addition, although the following items are not terms for the clinical hold, we request that you provide responses to them.

1. Please explain why lactation was seen in the mammary gland of one treated female dog.

2. Since SCH 58235 is a lipophilic drug similar to SCH 48461, please submit a tissue distribution study using radio-labeled drug to determine half-lives in the tissues. An HPLC profile using radio-labeled drug would provide data on the best animal model for humans.

3. The doses used in the 3-month dog study were too low to enable us to pinpoint target organs. In addition, possibly by waiting up to two hours post-feeding to dose, plasma exposure was also kept low. Dogs should be 4 to 6 months old at the beginning of the 1-year toxicity study (Redbook, 1993) vs. 12 to 13 months old as they were here. Please submit a protocol for a short-term dog study with dogs dosed as in IND 42,075 (up to 3,000 mg/kg/day by gavage in methylcellulose).

4. The histopathology in the 3-month rat study showed control rats with problems in the kidneys, lymph nodes, liver, heart, thyroid, and lungs. Because of this high background incidence, it is difficult to pinpoint target organs and will be an increasing problem as the length of studies and ages of the rats increase. Please explain how you plan to address this issue.

5. The exposure in the 3-month dietary rat study was low. You may want to consider a gavage study like the one done with SCH 48461.

6. Finally, before carcinogenicity studies are begun, you should submit range-finding and carcinogenicity protocols.

Until you have submitted the required information, and we notify you that it is safe to initiate the trial, you may not legally conduct the study under this IND. Please identify your response to the clinical hold issues as an "IND HOLD RESPONSE" and clearly indicate that you have responded to all clinical hold issues in your cover letter. To facilitate a response to your submission, please submit this information in triplicate to the IND. In addition, please send a copy of the cover letter to Ms. Margaret Simoneau, R.Ph., at the address below:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

Following receipt of your complete response to these issues, we will notify you of our decision within thirty days. If you have any questions concerning this IND, please contact Ms. Margaret Simoneau, R.Ph., Consumer Safety Officer, at 301-443-3510.

Sincerely yours,

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

SCHERING CORPORATION

GALLOPING HILL ROAD KENILWORTH, N. J. 07033

CABLES: SCHERING KENILWORTH
TELEX: 138316
138280
TELEPHONE: (908) 298-4000

April 22, 1997

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products
HFD-510, Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

IND 52,791
Sch 58235
Cholesterol Inhibitor
Serial No. 001

SUBJECT: IND HOLD RESPONSE

Dear Dr. Sobel:

In response to your letter of April 5, 1997 placing IND 52,791 on clinical hold, we are providing the following information:

Pharmacokinetic data from the Rising Single Dose Study (I96-088) and Rising Multiple Dose Study (I96-139). The PK results from these two studies (**Attachment 1**) show that the extent of drug accumulation at steady state is about two-fold. This is in agreement with what is predicted from the single dose data for a drug with an effective elimination half-life of approx. 24 hours administered once-a-day.

As discussed on Monday April 7, 1997 between yourself and SPRI's Dr. Lamendola and Ms. Boyle, final safety data from these studies are not yet available but will be provided as soon as possible. No particular safety issues are apparent from preliminary review of the data. In order to address the safety concerns, in particular the "hepatotoxic' potential of SCH 58235, in this response we have updated the summary table of noteworthy liver enzyme elevations by including follow-up data for all subjects with elevations during study, as well as an assessment of these findings and a proposed action plan.

The data for the subjects in the rising multiple-dose study with noteworthy elevations in liver function parameters have been updated and are summarized in **Table 1** of **Attachment 2**. The degree of SGPT elevations observed in the subjects receiving active SCH 58235 tended to be higher than the two subjects who received placebo (**Table 1** and **Figure 1** of **Attachment 2**). Six of 8 active subjects had >2X increase in SGPT, whereas both placebo subjects had <=2X increase in SGPT. In view of

these data, the degree of LFT changes cannot be considered the same between active and placebo. However, in this same investigator site, there is a historical incidence of approx. 25% of placebo treated subjects in multiple dose studies having an unexplained increase in LFTs, with about 11% having >2X increase in LFTs (see **Attachment 2** for a copy of a letter from the Phase I investigator). We have no good explanation as to the cause of the transient increases in LFTs in healthy subjects (or patients for that matter) treated with placebo. We do know however, that it occurs in approx. 6% of subjects in single dose studies and 25% of subjects in multiple dose studies in this Phase I unit. In the sponsor's experience, this incidence appears to be similar to other Phase I units, although not as clearly documented. The theories for such observations include: diet changes, activity changes and normal variability in LFTs if these were monitored as closely in the general population as they are in these safety/tolerance trials.

Based on the above considerations and the limited clinical experience with this new agent, a causal relationship between SCH 58235 administration and elevations in liver function tests cannot be excluded. However, the fact that an obvious dose-response relationship is not present, the similar incidence reported for subjects receiving placebo, and the apparent lack of hepatotoxicity in the preclinical species tested suggest that this may not be a liability of the drug and should not preclude further clinical development of SCH 58235. However, we should be cautious and monitor patients carefully in the initial clinical trials until clinical safety experience with this compound suggests that "hepatotoxicity" is not a liability and does not warrant intensive patient monitoring.

The suggested action plan by the sponsor is for the next few clinical trials to intensely monitor patients for evidence of "hepatotoxicity". Towards this goal, we are amending the clinical study protocol (C95-345, **Attachment 3**) to implement procedures to monitor for and address any abnormalities in liver function tests.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

MJB:ms
Desk Copy: Ms. Margaret Simoneau
I:\usra\ind\52791\letter\001.mjb

DISTRIBUTION

IND 52,791
Cholesterol Inhibitor

Mr. Affrime	K-15-4	4455
Dr. Batra	K-15-2	2650
Ms. Boyle*	L-6-1	1635
Dr. Cuffie	K-15-3	3005
DeAngelis	K-11-3	L-5
Dr. Giaquinto	K-6-1	1330
Dr. Halliwell	Laf.	
Dr. Kosoglou *	K-15-4	4455
Mr. Lauda	K-6-2	D-22
Dr. Lamendola	K-6-1	1345
Dr. Lipka	K-15-3	3035
Dr. Patrick*	K-15-2	2880
Dr. Ress*	K-15-4	4025
Dr. Spicehandler	K-15-4	
Dr. Spiegel	K-15-4	4305

RA File*
Product File

*Complete

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014
Expiration Date: November 30, 1995.
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. NAME OF SPONSOR
Schering Corporation

2. DATE OF SUBMISSION
April 22, 1997

3. ADDRESS *(Number, Street, City, State and Zip Code)*
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

4. TELEPHONE NUMBER *(Include Area Code)*
(908) 298-2628

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
SCH 58235 CAPSULES

6. IND NUMBER *(If previoulsy assigned)*
52791

7. INDICATION(S) *(Covered by this submission)*
Hypercholesterolemia

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED ☐ PHASE 1 ■ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION
None

10. *IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.*

SERIAL NUMBER: 0 0 1

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
■ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY / MICROBIOLOGY
☐ PHARMACOLOGY / TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED. ☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND, 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL, 21 CFR 312.35(b) ☐ CHARGE REQUEST NOTIFICATION, 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/OGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

24360019

CONTENTS OF APPLICATION

This application contains the following items: *(check all that apply)*

- ■ 1. Form FDA 1571 *[21 CFR 312.23 (a) (1)]*
- ☐ 2. Table of contents *[21 CFR 312.23 (a) (2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23 (a) (3)]*
- ☐ 4. General investigational plan *[21 CFR 312.23 (a) (3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23 (a) (5)]*
- 6. Protocol(s) *[21 CFR 312.23 (a) (6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23 (a) (6)]*
  - ☐ b. Investigator data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23 (a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23 (a) (7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23 (a) (7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23 (a) (8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23 (a) (9)]*
- ☐ 10. Additional information *[21 CFR 312.23 (a) (10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ■ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ■ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Cynthia Cuffie, M.D.
Distinguished Clinical Research Physician
Cardiovascular, Dermatology, Endocrinology

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Robert J. Spiegel, M.D.
Senior Vice President
Worldwide Clinical Research

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Joseph F. Lamendola, Ph.D. Vice President, U.S. Regulatory Affairs	Mary Jane Boyle	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
2000 Galloping Hill Road Kenilworth, New Jersey 07033	(908) 298-2628	4/22/97

(WARNING: A willfully false statement is a criminal offense U S C Title 18, Sec. 1001)